REMARKS

I. Rejection of claims 1 and 9 under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1 and 9 under 35 U.S.C. § 103(a) as allegedly being obvious over Whitmarsh et al. (Molecular Human Reproduction, Vol. 2, No. 12, pgs. 911-919) in view of Chamberlin and Dean (Proceedings of the National Academy of Science, USA, Vol. 87, pgs. 6014-6018, Aug. 1990). The Whitmarsh reference is relied on in the Action for teaching a method of measuring the biological activity of recombinant human ZP3 (rhZP3). Chamberlin and Dean is relied on in the Action for teaching hZP3 expressed from human ovaries. The Examiner asserts that it would have been obvious to employ a human ZP3 expressed from human ovaries as taught by Chamberlin and Dean in the method of Whitmarsh et al. to measure ZP3 and sperm binding as an indicator of sperm affinity. Applicants respectfully traverse this rejection because claims 1 and 9 are not obvious over Whitmarsh et al. in view of Chamberlin and Dean for the reasons discussed below.

To properly make a rejection under 35 U.S.C. § 103, the Examiner has the initial burden of establishing a *prima facie* case of obviousness. Meeting this burden requires the Examiner to show first, that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process. Second, the Examiner must establish that the prior art would have revealed that in so making or carrying out the claimed process, those of ordinary skill in the art would have had a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the

prior art, not in Applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), citing *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

As stated above, Whitmarsh et al. discloses a method of measuring the biological activity of rhZP3. The primary purpose of the Whitmarsh et al. study, as described on pages 911-912, is to use the in vitro transcription and translation system to produce immobilized rhZP3 on agarose beads and to examine the biological activity of the rhZP3 using sperm binding and acrosome reaction data. However, Whitmarsh et al. does not disclose or suggest the use of *properly glycosylated* hZP3 in order to determine human sperm activity. The Examiner asserts that Whitmarsh et al. provides the means by which the rhZP3 can be glycosylated by mentioning the possible incorporation of canine pancreatic microsomal membranes. Applicants respectfully submit that the incorporation of these membranes would not, in fact, result in a properly glycosylated, biologically active rhZP3. As described in the present specification, glycosylation is tissue-and species-specific. Furthermore, Applicants have found that only in human cell lines can a properly glycosylated ZP3 protein be produced that has both the sperm-binding activity and acrosome reaction-inducing functions of native hZP3. Therefore, the use of canine pancreatic microsomal membranes, as suggested by Whitmarsh et al, would have resulted in a rhZP3 with a different glycosylation pattern than that of the present invention. In addition, a rhZP3 glycopolypeptide produced by such canine membranes would not possess full biological activity with human sperm in contrast to the rhZP3 of the present invention.

Furthermore, Whitmarsh et al. does not address the importance of a properly glycosylated rhZP3. For instance, in observing that the median level of sperm binding to its rhZP3 beads is low, Whitmarsh et al. proposes several reasons on page 916 as to why this may be the case.

However, Whitmarsh et al. never suggests that its rhZP3's lack of glycosylation may have been the reason for such low binding results. Similarly, on page 917, Whitmarsh et al. also speculates as to why the acrosome reactions were induced only after long incubation times. Again, Whitmarsh et al. never discloses that the rhZP3's lack of glycosylation could be the reason that such long incubation times were necessary. In fact, Whitmarsh et al. teaches away from the importance of the glycosylation of the human ZP3 protein by contrasting it with the mouse ZP3 protein. As pointed out by the Examiner, Whitmarsh et al. mentions the importance of carbohydrates in the binding of spermatozoa to the mouse zona pellucida at page 917. However, since the rhZP3 in Whitmarsh et al. exhibited some biological activity, while lacking glycosylation, Whitmarsh et al. contrasts the human ZP3 with the mouse ZP3 in stating:

> The situation in the human is however more complex where the protein backbone also plays a significant role. . . We therefore think that the protein backbone of ZP3 may have a more significant role to play in sperm binding and subsequent acrosome reaction in human than in mouse. We are examining further the role of the protein backbone in human gamete recognition.

Therefore, Whitmarsh et al. downplays the importance of a properly glycosylated rhZP3 protein and does not disclose or suggest a method of determining sperm activity using a glycosylated rhZP3 expressed by a human ovarian cell.

The Examiner further asserts that Chamberlin and Dean teach a rhZP3 expressed from human ovaries. The Examiner is referring to page 6015 where Chamberlin and Dean describe the purification of Poly(A)$^+$ RNA from total RNA isolated from a human ovary. Applicants respectfully submit that this disclosure does not, in fact, disclose or suggest rhZP3 *expressed* from a human ovarian cell. Chamberlin and Dean merely isolated ZP3 RNA from a human ovary; however, Chamberlin and Dean did not isolate or produce a ZP3 *protein* expressed from a

human ovarian cell. In fact, Chamberlin and Dean did not isolate or produce any ZP3 proteins at all. Chamberlin and Dean simply used the isolated RNA to produce hZP3 cDNA via PCR techniques. This cDNA was then sequenced and a computer was used to subsequently deduce the hZP3 amino acid sequence. Hence, Chamberlin and Dean never actually isolated or produced a ZP3 protein. Furthermore, the isolation of ZP3 RNA from a human ovary does not teach a properly glycosylated hZP3 *expressed from* a human ovarian cell. Since the RNA is never translated into a protein, there is no glycosylation of this RNA. As described in the present specification, the post-translational activities of the human ovarian cell are highly important as optimal glycosylation is a crucial step in producing a biologically active hZP3. Therefore, based on Chamberlin and Dean, it would not have been obvious to one of ordinary skill in the art to express a rhZP3 protein from a human ovarian cell.

Furthermore, one of ordinary skill in the art would not have a had a reasonable expectation of success in expressing a biologically active rhZP3 from a human ovarian cell. As described in the present application at page 27, because hZP3 has a strong hydrophobic backbone, as well as large carbohydrate side chains, it is extremely difficult to produce the hZP3 glycoprotein by recombinant DNA technology. As described in the specification on page 27, various groups (including Whitmarsh et al.), have attempted to produce rhZP3; however, no one has been able to produce a rhZP3 with full biological activity as measured by the ability to bind sperm and to induce an acrosome reaction. Applicants, for the first time, have produced a rhZP3 which possesses both the ability to bind human sperm, as well as the ability to induce an acrosome reaction, in a manner similar to that of native hZP3.

Hence, Whitmarsh et al. and Chamberlin and Dean do not disclose the expression of recombinant human ZP3 from human ovarian cells. Therefore, Whitmarsh et al. and Chamberlin and Dean do not disclose the binding assay of claims 1 or 9. Accordingly, the present invention would not have been obvious to one of ordinary skill in the art and Applicants respectfully request that the rejection of claims 1 and 9 be withdrawn.

II. <u>Rejection of claims 2-8 under 35 U.S.C. § 103(a)</u>

Claims 2-8 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Whitmarsh et al. (Molecular Human Reproduction, Vol. 2, No. 12, pgs. 911-919) in view of Chamberlin and Dean (Proceedings of the National Academy of Science, USA, Vol. 87, pgs. 6014-6018, Aug. 1990). As stated above, Whitmarsh et al. is relied on in the Action for teaching a method for measuring the biological activity of rhZP3 and Chamberlin and Dean is relied on for teaching a human ZP3 expressed from human ovaries. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the concentration of the reagents to the specific concentrations recited in claims 2-8. Applicants respectfully traverse this rejection because claims 2-8 are not obvious over Whitmarsh et al. in view of Chamberlin and Dean for the reasons discussed below.

Whitmarsh et al. and Chamberlin and Dean do not disclose or suggest the binding assay of claim 1 for the reasons discussed above. Therefore, since Whitmarsh et al. and Chamberlin and Dean do not disclose or suggest the binding assay of the presently claimed invention, the various concentrations of the human ZP3 protein in claims 2-8 would not have been obvious to

one of ordinary skill in the art at the time the invention was made. Applicants respectfully request that the rejection be withdrawn.

III. Rejection of claim 19 under 35 U.S.C. § 103(a)

The Examiner has rejected claim 19 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Whitmarsh et al. in view of Chamberlin and Dean and further in view of Foster et al. (U.S. Patent No. 4,444,879). As stated above, Whitmarsh et al. is relied on in the Action for teaching a method for measuring the biological activity of rhZP3 and Chamberlin and Dean is relied on for teaching a human ZP3 expressed from human ovaries. Foster et al. is relied on in the Action for teaching kits including reactant reagents, a micro plate, positive controls, negative controls, standards, and instructions. The Examiner asserts that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to take the binding/detection assay as taught by Whitmarsh et al. in view of Chamberlin and Dean and format them into a kit because Foster et al. teach that it is convenient to do so and one can enhance sensitivity of a method by providing reagents as a kit.

Applicants respectfully submit that Whitmarsh et al. does not disclose or suggest the claimed invention for the reasons set forth above. In particular, Whitmarsh et al. does not disclose or suggest a diagnosis kit comprising glycosylated rhZP3 expressed from a human ovarian cell. Whitmarsh et al. teaches away from the importance of glycosylation in sperm binding and provides no suggestion or disclosure of the importance of the expression of rhZP3 from a human ovarian cell in order to possess full biological activity.

Furthermore, Chamberlin and Dean also do not disclose or suggest the diagnosis kit of the presently claimed invention. Chamberlin and Dean do not demonstrate the expression of any rhZP3 protein, let alone the expression of a hZP3 from a human ovarian cell. Chamberlin and Dean simply isolate some RNA from a human ovary. As such RNA has not been translated into a protein, this RNA will necessarily lack the carbohydrate side chains, which are applied post-translationally by the ovarian cell's glycosylation machinery. Therefore, Chamberlin and Dean do not provide any disclosure or suggestion of a diagnosis kit comprising a glycosylated rhZP3 expressed from a human ovarian cell.

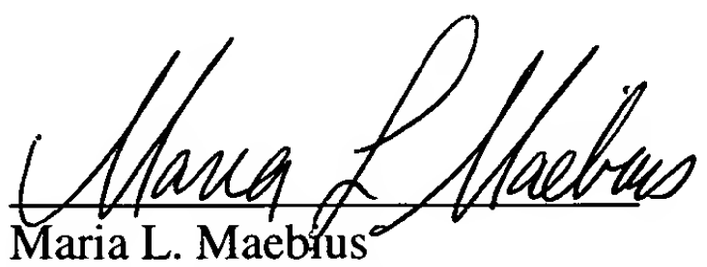
The Foster patent does not remedy the deficiencies of the Whitmarsh et al. or Chamberlin and Dean references. The Foster patent discloses an assay reagent kit comprising a microtiter plate, a supply of various immunoglobins such as IgE, buffer wash solutions, enzyme-labeled anti-Ig conjugate, enzyme specific substrate, positive and negative controls, standards and instructions. The Foster patent does not describe or suggest a diagnostic kit for sperm activity comprising compartments with glycosylated recombinant human ZP3, expressed from a human ovarian cell, and one or more reagents listed in claim 19.

Accordingly, Applicants assert that none of the references, taken alone or in combination, describe or suggest the presently claimed invention of claim 19. Applicants respectfully request that the rejection be withdrawn.

IV. CONCLUSION

In view of the foregoing remarks, Applicants believe that the application is in condition for allowance. However, if the Examiner disagrees, she is encouraged to call the undersigned at the number listed below in order to expedite the prosecution of this application.

Respectfully submitted,



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